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Medical conditions associated with gastroduodenal ulceration or erosion in 168 dogs: 2008-2018

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Abstract

Background: Many medical conditions are thought to cause gastroduodenal ulceration or erosion (GUE) in dogs. However, evidence for the association between many of these conditions and GUE in dogs is lacking.

Objective: To identify medical conditions associated with GUE in dogs.

Animals: One hundred and sixty-eight dogs with GUE and 168 randomly selected control dogs without evidence of GUE identified on necropsy between January 2008 and September 2018.

Methods: Patient signalment, blood urea nitrogen (BUN) and serum creatinine concentrations, recently administered ulcerogenic drugs, as well as necropsy findings were recorded. The association between these findings and presence of GUE was assessed by univariable and multivariable analysis.

Results: In the final multivariable model, the following factors were associated with GUE: Nonsteroidal anti-inflammatory drug (NSAID) administration (odds ratio [OR], 6.3; 95% confidence interval [CI], 2.3-17.4; $P = .0004$), glucocorticoid administration (OR, 3.0; 95% CI, 1.5-5.9; $P = .001$), gastrointestinal neoplasia (OR, 13.5; 95% CI, 1.7-108.0; $P = .01$) and gastrointestinal mechanical disease (foreign bodies, gastric dilatation, and volvulus; OR, 4.8; 95% CI, 1.2-19.7; $P = .03$). Additionally, working dog breeds were predisposed to GUE compared to mixed breed dogs (OR, 2.8; 95% CI, 1.1-7.4; $P = .04$). Insufficient clinical data was available to either support or refute a role of other putative risk factors evaluated.

Conclusion and Clinical Importance: Administration of NSAID or glucocorticoid and gastrointestinal neoplasia or mechanical disease were associated with GUE in dogs. The potential predisposition of working breed dogs for GUE requires further investigation.

KEYWORDS
gastroduodenal erosion, gastroduodenal ulceration, gastrointestinal neoplasia, glucocorticoid, NSAIDs

Abbreviations: AKC, American Kennel Club; CNS, central nervous system; DIC, Disseminated intravascular coagulopathy; GI, gastrointestinal; GUE, gastroduodenal ulceration or erosion; IRIS, International Renal Interest Society; NSAID, nonsteroidal anti-inflammatory drug.

1 | INTRODUCTION

Gastroduodenal ulceration and erosion (GUE) is a clinical concern in dogs, and its incidence is not known. Signs of GUE include vomiting, abdominal pain, hematemesis, or melena.[1,2] This condition can lead to severe gastrointestinal bleeding necessitating blood transfusions or surgical intervention, and, untreated, can result in death. However, early clinical signs can be vague or subtle.[2-4] Moreover, the diseases predisposing dogs to GUE have been poorly defined. A better understanding of predisposing diseases would be beneficial for patient monitoring and allow for earlier intervention or prophylaxis. In a previous retrospective case series in which dogs with gastric ulceration or perforation were evaluated, potential predisposing factors frequently were reported to include administration of nonsteroidal anti-inflammatory drugs (NSAIDs), gastrointestinal neoplasia, or hepatobiliary disease.[2-4] However, in these studies, a control population of dogs without GUE was not included and thus an association between the putative predisposing factors and GUE could not be determined. Indeed, for many of these conditions, insufficient evidence was available to critically evaluate if they predisposed dogs to GUE.[5]

In these case series, antemortem tests (eg, radiology, endoscopy, surgery) were most commonly used to identify dogs with gastroduodenal ulceration or perforation and to describe their comorbidities, response to treatment, and outcome.[2-4] Often, these studies were limited to small groups of dogs.

To our knowledge, no controlled observational studies have been performed to determine the association between many of the putative predisposing factors and GUE in dogs. Therefore, our objective was to investigate the association between putative predisposing factors and necropsy-confirmed GUE in dogs using a retrospective case-control design.

2 | MATERIALS AND METHODS

2.1 | Dogs with gastric ulceration

Because medical records were reviewed retrospectively, institutional animal care and use committee approval and informed client consent were not required.

Dogs with necropsy-confirmed GUE diagnosed between January 10, 2008 and September 30, 2018 were identified by an electronic search of the database of Texas A&M Veterinary Medical Teaching Hospital using the keywords "gastric," "gastritis," "duodenal," "duodenitis," "enteritis," "erosive," "erosion," "ulcer," "ulcerative," and "ulceration." The medical record was reviewed for each dog identified. Dogs without recorded evidence of GUE or without adequate medical record documentation were excluded.

Necropsies were supervised by a board-certified or residency-trained veterinary anatomic pathologist and included a complete gross examination and histopathological assessment of tissues of interest.

2.2 | Control dogs

Dogs that had no evidence of GUE recorded during necropsy over the same time period were randomly selected in a 1 : 1 ratio with cases.

2.3 | Data collection and review

Each medical record, including the necropsy report, was reviewed by a small animal internal medicine resident (EP) and the following data were recorded: signalment, CBC and serum biochemistry profile results (when available), medications administered the week before death. Dosages of administered NSAIDs and glucocorticoids were recorded. The time frame of 7 days was chosen to ensure a temporal relationship between factors and GUE. Each dog was assigned to an American Kennel Club (AKC) breed[6] or mixed breed group as appropriate. Where the medical record stated that the patient had disseminated intravascular coagulation (DIC), sepsis, or shock, these conditions were recorded. Where serum biochemistry had been performed within 7 days of necropsy, serum creatinine and blood urea nitrogen (BUN) concentrations were recorded, as well as the reference interval for the instrument used. Because of the frequent lack of available urinalyses, the classification of azotemia as prerenal, renal, or postrenal could not be made. Necropsy diagnosis and the location of the ulcer or erosion (if present), as well as pathologic findings within organ systems (eg, kidneys, liver, gastrointestinal [GI] tract, central nervous system [CNS]), and the presence of neoplasia (in any tissue) were recorded.

Putative predisposing factors were documented from the clinical record and necropsy report. Necropsy findings were divided into the following categories: renal disease, GI disease, hepatobiliary disease, neurologic disease, and neoplasia (in any tissue). The diagnosis of renal disease was based on necropsy findings (including histology). In the absence of other signs, mild interstitial nephritis was not considered renal disease. Neoplasia also was subdivided into specific types: carcinomas, lymphoma or leukemia, hemangiosarcoma, mast cell tumor, histiocytic sarcoma, and "other." Gastrointestinal diseases were subdivided into neoplasia of the GI tract, inflammatory bowel disease or lymphangiectasia, intestinal parasites, other infectious diseases (viral, bacterial, fungal), and mechanical causes (foreign bodies, gastric dilatation volvulus). Hepatobiliary diseases were subdivided into the following groups: hepatobiliary neoplasia, chronic hepatitis, acute hepatopathy (including toxins), infectious liver disease, congenital portosystemic shunts, and "other" (uncharacterized hepatopathies, bridging fibrosis without concurrent necroinflammatory activity, hepatocellular atrophy). In the absence of other signs, reactive hepatopathies, vacuolar hepatopathy, and regenerative changes were not considered to be diagnostic for hepatobiliary disease.

2.4 | Data analysis

Continuous data were assessed for normality using a Kolmogorov-Smirnov test and visual inspection of frequency distribution histograms. Differences in continuously distributed data between dogs with

and without gastric or duodenal ulceration were assessed using *t* tests for parametric data and Wilcoxon tests for nonparametric data. The association between sexual status and breed group as well as other categorical variables and GUE initially was assessed using univariable analysis with Fisher's exact tests. Characteristics with a univariable P value < .2 were entered into a multivariable logistic regression model. A final multivariable model then was constructed using backwards stepwise elimination. Model fit was assessed using Akaike information criteria, Bayesian information criteria and Chi-squared goodness-of -fit tests. Mixed breed dogs were considered to be the referent group for breed group analysis. *P*-values < .05 were considered to be statistically significant. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Confounding was assessed by determining if individual variable ORs changed by >20% with inclusion or removal of additional variables. Analysis was performed using a commercially available statistical software package (JMP v15, SAS, Cary, NC, USA).

3 | RESULTS

3.1 | Dogs with gastroduodenal ulceration

An initial search for dogs that had gastric or duodenal ulceration or erosion found on necropsy yielded 169 cases. One dog was excluded because of lack of available medical record (a dog from a research colony), leaving 168 cases with GUE (Table 1). Of these 168 cases, 34 dogs were intact males (20.2%), 48 were castrated males (28.6%), 68 were spayed females (40.5%), and 18 dogs were intact females (10.7%). The dogs ranged in age from 3 months to 19 years (median, 8 years). A wide variety of breeds was represented; the most common breeds were Labrador retrievers (16.7%), mixed breed dogs (8.9%), golden retrievers (5.4%), and boxers (4.8%). The most common AKC breed groups were: 47 (28.0%) sporting dogs, 32 (19.0%) working dogs, and 20 (11.9%) herding dogs.

One hundred and forty-eight (88.1%) dogs had ulcers or erosions in the stomach, 10 (6.0%) dogs had ulcers or erosions in both the stomach and duodenum, and 20 dogs (11.9%) had ulcers or erosions in the duodenum alone. Of the dogs that had ulcers or erosions in the stomach, 91 dogs had affected regions of the stomach specifically noted on the necropsy report. Twenty-seven dogs (29.7%) had ulcers or erosions in the pylorus, 11 dogs (12.1%) had ulcers or erosions in the body, 10 dogs (11.1%) had ulcers or erosions in the fundus, 10 (11.1%) along the greater curvature, 3 (3.3%) had ulcers or erosions in the cardia, 2 (2.2%) along the lesser curvature, and 1 (1.1%) ulcer or erosion was noted in the antrum. Twenty-seven dogs (29.7%) had ulcers or erosions in >1 location in the stomach.

In the week before death, 28 dogs (16.7%) had received a NSAID and 45 dogs (26.8%) had received a glucocorticoid. Six dogs (1.8%) had received both an NSAID and a glucocorticoid. Thirty-two dogs (19.0%) were noted to have been in DIC, shock, or sepsis before death; insufficient data was found in the record to determine whether or not these syndromes were present in the 136 remaining dogs

TABLE 1 Univariable analysis of the association between antemortem variables and the presence of gastroduodenal ulceration or erosion on necropsy in 336 dogs

Antemortem variables		Dogs with gastroduodenal ulceration or erosion (n = 168)	Dogs without gastroduodenal ulceration or erosion (n = 168)	Odds ratio (95% CI)	*P*-value
Median age (min–max)		8 years (0.25-19)	8 years (0.003-17)	NA	.75
Sex	Female intact	18 dogs (10.7%)	22 dogs (13.1%)	NA	.1
	Female spayed	68 dogs (40.5%)	64 dogs (38.1%)		
	Male intact	34 dogs (20.2%)	33 dogs (19.6%)		
	Male castrated	48 dogs (28.6%)	49 dogs (29.2%)		
AKC breed group	Mixed breed	15 dogs (8.9%)	21 dogs (12.5%)	NA	.0005
	Sporting	47 dogs (28%)	35 dogs (20.8%)		
	Hounds	20 dogs (11.9%)	18 dogs (10.7%)		
	Working	32 dogs (19%)	13 dogs (7.7%)		
	Terriers	18 dogs (10.7%)	17 dogs (10.1%)		
	Toys	9 dogs (5.4%)	31 dogs (18.5%)		
	Nonsporting	7 dogs (4.2%)	15 dogs (8.9%)		
	Herding	20 dogs (11.9%)	18 dogs (10.7%)		
DIC/Sepsis/shock		32 dogs (19%)	23 dogs (13.7%)	NA	NA
NSAID administration		28 dogs (16.7%)	5 dogs (3%)	6.5 (2.5-17.3)	< .0001
Glucocorticoid administration		45 dogs (26.8%)	16 dogs (9.5%)	3.4 (1.9-6.4)	< .0001
Azotemia		31/134 dogs (23.1%)	18/103 dogs (17.5%)	1.4 (0.7-2.7)	.33

Note: The denominator for each percentage is 168 unless otherwise stated. As DIC, shock, or sepsis could not be ruled out for many dogs from their medical records it was not possible to assess the association of this variable and the presence of gastroduodenal ulceration or erosion.
Abbreviations: CI, confidence interval; NA, not applicable.

(81.0%). For the 134 dogs that had serum biochemistry performed in the week before death, 31 dogs (23.1%) were azotemic (defined as a serum creatinine concentration ≥ 1.4 mg/dL, based on International Renal Interest Society [IRIS] staging guidelines). The median serum creatinine concentration for all dogs for which laboratory results were available in the record was 0.9 mg/dL (range, 0.4 to >20.0 mg/dL). Six dogs with GUE had received either a proton pump inhibitor or an H_2 receptor blocker antemortem.

The most common pathologic findings in dogs with GUE on necropsy included neoplasia (of any tissue; 64 dogs, 38.1%), hepatobiliary disease (52 dogs, 31.0%), renal disease (47 dogs, 28.0%) and gastrointestinal disease (44 dogs, 26.2%; Table 2).

Neoplasia found in the body of the stomach was further subdivided into specific types: carcinomas (22 dogs, 13.1%), lymphoma or leukemia (14 dogs, 8.3%), hemangiosarcoma (10 dogs, 6.0%), histiocytic sarcoma (5 dogs, 3.0%), mast cell tumors (5 dogs, 3.0%), and other (10 dogs, 6.0%). This category also included individual dogs with osteosarcoma, pheochromocytoma, peripheral nerve sheath tumor, chemodectoma, meningioma, or polycythemia vera.

Dogs with hepatobiliary disease were further subdivided into the following groups: neoplasia of the liver (22 dogs, 13.1%), chronic hepatitis (5 dogs, 3.0%), acute hepatopathy, including toxins (9 dogs, 5.4%), infectious liver disease (5 dogs, 3.0%), and other (uncharacterized chronic hepatopathies, bridging fibrosis, or cellular atrophy without a clear underlying cause noted on necropsy; 15 dogs, 8.9%). No dogs in this group were diagnosed with congenital portosystemic shunts.

Gastrointestinal diseases were further subdivided into the following categories: neoplasia of the GI tract (13 dogs, 7.7%), inflammatory bowel disease or lymphangiectasia (6 dogs, 3.6%), intestinal parasites (7 dogs, 4.2%), mechanical causes (such as gastric dilatation and volvulus or foreign bodies; 9 dogs, 5.4%), other infectious causes (viral, bacterial, or fungal; 8 dogs, 4.8%), and other undefined process (1 dog, 0.6%, with "nonclostridial necrotizing enteritis").

Fourteen dogs did not have putative predisposing factors recorded. Among these, 4 dogs had acute trauma, 3 had aspiration pneumonia, and 2 had severe infections (bacterial cellulitis, encephalitis).

TABLE 2 Univariable analysis of the association between postmortem variables and the presence of gastroduodenal ulceration or erosion on necropsy in 336 dogs

Necropsy findings	Dogs with gastroduodenal ulceration or erosion (n = 168)	Dogs without gastroduodenal ulceration or erosion (n = 168)	Odds ratio (95% CI)	*P*-value
Neoplasia	64 dogs (38.1%)	48 dogs (28.6%)	1.5 (1-2.43)	.08
Mast cell tumors	5 dogs (3%)	1 dog (0.6%)	5.1 (0.6-44.3)	.21
Lymphoma	14 dogs (8.3%)	4 dogs (2.4%)	3.7 (1.2-11.6)	.03
Hemangiosarcoma	10 dogs (6%)	10 dogs (6%)	1 (0.4-2.5)	1
Histiocytic sarcoma	5 dogs (3%)	3 dogs (1.8%)	1.7 (0.4-7.2)	.72
Carcinoma	22 dogs (13.1%)	16 dogs (9.5%)	1.4 (0.7-2.8)	.39
Other	10 dogs (6%)	14 dogs (8.3%)	0.7 (0.3-1.6)	.53
Hepatobiliary disease	52 dogs (31%)	38 dogs (22.6%)	1.5 (0.9-2.5)	.11
Hepatobiliary neoplasia	22 dogs (13.1%)	11 dogs (6.6%)	2.2 (1-4.6)	.07
Chronic hepatitis	5 dogs (3%)	3 dogs (1.8%)	1.7 (0.4–7.2)	.72
Acute hepatopathy	9 dogs (5.4%)	7 dogs (4.2%)	1.3 (0.5-3.6)	.8
Infectious	5 dogs (3%)	4 dogs (2.4%)	1.3 (0.3-4.8)	1
Congenital portosystemic shunt	0 dog (0%)	1 dog (0.6%)	NA	1
Other	15 dogs (8.9%)	12 dogs (7.1%)	1.3 (0.6-2.8)	.64
Gastrointestinal disease	44 dogs (23.2%)	31 dogs (18.5%)	1.6 (0.9-2.6)	.12
Gastrointestinal neoplasia	13 dogs (7.7%)	1 dog (0.6%)	14 (1.8-108.3)	.002
Inflammatory bowel disease/ lymphangiectasia	6 dogs (4.2%)	6 dogs (3%)	1 (0.3-3.2)	1
Gastrointestinal parasites	7 dogs (4.2%)	7 dogs (4.2%)	1 (0.3-2.9)	1
Other infectious	8 dogs (4.8%)	11 dogs (6.6%)	0.7 (0.3-1.8)	.64
Mechanical	9 dogs (5.4%)	3 dogs (1.8%)	3.1 (0.8–11.7)	.14
Undefined	1 dog (0.6%)	4 dogs (2.4%)	0.2 (0.03-2.22)	.37
Renal disease	47 dogs (28%)	44 dogs (26.2%)	1.1 (0.7-1.8)	.81
Neurologic disease	27 dogs (16.1%)	34 dogs (20.2%)	1.8 (0.4-1.3)	.4

Abbreviations: CI, confidence interval; NA, not applicable.

3.2 | Control dogs

One hundred and sixty-eight randomly selected control dogs without GUE were identified (Table 1). Of these 168 dogs, 33 were intact males (19.6%), 49 were castrated males (29.2%), 64 were spayed females (38.1%), and 22 were intact females (13.1%). The dogs ranged in age from 1 day old to 17 years (median, 8 years). A wide variety of breeds was represented; the most common breeds were mixed breed (12.5%), Labrador retrievers (11.9%), dachshunds (5.9%) and chihuahuas (5.9%). The most commonly represented breed groups were: 35 (20.8%) sporting dogs, 31 (18.5%) toy dogs, and 21(12.5%) mixed breed dogs.

In the week before death, 5 dogs (3%) had received NSAIDs and 16 dogs (9.5%) had received glucocorticoids. Five dogs (3%) had received both glucocorticoids and NSAIDs. Twenty-three dogs (13.7%) were noted to have been in DIC, shock, or diagnosed with sepsis before death, 4 dogs (2.4%) were determined not to have DIC, shock, or sepsis and, for the remaining 141 dogs (83.9%), insufficient information was available to determine whether or not these syndromes were present. Of the 102 dogs that had laboratory tests performed in the week before death, 18 dogs (17.7%) were azotemic. The median serum creatinine concentration for the control group was 0.8 mg/dL (range, 0.4-15.3 mg/dL). In the control group, 1 dog had received pantoprazole and one dog received sucralfate antemortem.

The most common pathological findings at necropsy included neoplasia (of any tissue; 48 dogs, 28.6%), renal disease (44 dogs, 26.2%), hepatobiliary disease (38 dogs, 22.6%), neurologic disease (34 dogs, 20.2%), and GI disease (31 dogs, 18.5%; Table 2).

3.3 | Univariable analysis

The results of the univariable analysis were divided into antemortem clinical variables (age, sex, AKC breed group, presence of azotemia, and administration of NSAID or glucocorticoid before death) and necropsy pathological findings (diagnosis of renal disease, neoplasia, hepatobiliary disease, GI disease, or neurologic disease and their respective subcategories).

Of the antemortem clinical variables, breed group ($P = .0005$), NSAID administration ($P < .0001$), and glucocorticoid administration ($P < .0001$) were significantly associated with GUE (Table 2). Age, sex, and the presence of azotemia were not significantly associated with GUE ($P > .05$ for all; Table 1). There was too much missing data to evaluate the association of a diagnosis of DIC, shock or sepsis with GUE.

Of the necropsy findings, only the diagnosis of lymphoma or leukemia ($P = .03$) and gastrointestinal neoplasia ($P = .002$) were significantly associated with GUE. Of the cases with GI neoplasia, 6 dogs had primary gastric carcinoma and 3 dogs had metastatic carcinomas affecting their stomach or duodenum. Only 1 dog had primary gastric lymphoma; 3 dogs had disseminated lymphoma affecting their stomach. None of the other categories (renal disease, neurologic disease, hepatobiliary disease, or the additional subcategories of gastrointestinal disease or neoplasia) were significantly associated with GUE.

TABLE 3 Final multivariable model showing findings associated with gastroduodenal ulceration or erosion on necropsy in 336 dogs

Variable	Odds ratio (95% CI)	*P*-value
NSAID administration	6.3 (2.3-17.3)	.0004
Glucocorticoid administration	3 (1.5-5.9)	.001
AKC breed group[a]	NA	.01
Sporting	1.3 (0.6-3.1)	.53
Hounds	1 (0.4-2.8)	.96
Working	2.8 (1.1–7.4)	.03
Terriers	1.5 (0.6-4)	.41
Toy	0.5 (0.2-1.3)	.14
Nonsporting	0.5 (0.2-1.6)	.23
Herding	1.2 (0.5-3.3)	.69
Mixed breed	1	Reference
Gastrointestinal neoplasia	13.5 (1.7-108)	.01
GI mechanical	4.8 (1.2-19.7)	.03

Abbreviations: CI, confidence interval; NA, not applicable.
[a]Mixed breed dogs were used as the referent value for calculation of odds ratios and their respective *P*-values.

3.4 | Multivariable analysis

American Kennel Club group, NSAID administration, glucocorticoid administration, GI neoplasia, lymphoma or leukemia, hepatobiliary neoplasia, and GI mechanical disease were entered into the initial multivariable model (univariable $P < .2$). After backward stepwise elimination, the administration of NSAIDs (OR, 6.09; 95% CI, 2.21-16.80; $P = .0005$), administration of glucocorticoids (OR, 2.86; 95% CI, 1.46-5.57; $P = .002$), presence of GI neoplasia (OR, 12.70; 95% CI, 1.59-101.67; $P = .02$), GI mechanical disease (OR, 4.8; 95% CI, 1.2-19.7; $P = .03$), and being in AKC group 3-Working dogs (OR, 2.87; 95% CI, 1.09-7.52; $P = .03$, compared to mixed breed dogs) were associated with GUE (Table 3). When administration of glucocorticoids was included in the model, the diagnosis of lymphoma or leukemia was no longer associated with GUE, (initial OR, 3.7; 95% CI, 1.2-11.6; $P = .01$ vs OR with glucocorticoid administration, 0.4; 95% CI, 0.1-1.5; $P = .18$) suggesting confounding.

If the broader groups of neoplasia, GI disease, and hepatobiliary disease were entered in the model (instead of GI neoplasia, lymphoma or leukemia, hepatobiliary neoplasia, and GI mechanical disease) after backwards stepwise elimination, administration of NSAIDs, administration of glucocorticoids, being in AKC group 3-Working dogs, and the presence of GI disease were associated with GUE. However, model fit was not as good as when subgroups were used as described above.

4 | DISCUSSION

Successful treatment of GUE relies on early recognition. Many disease processes are suspected to predispose dogs to GUE, including GI disease, neoplasia, renal disease, or hepatobiliary disease.[2,7-10] However, few studies have evaluated the association between these factors and GUE in

comparison to a control group. Moreover, previous case series contained relatively small numbers of dogs.[2-4] Our objective was to assess the association between putative predisposing factors in dogs with necropsy-confirmed GUE using a retrospective case–control study design.

We found that recent NSAID and glucocorticoid administration were associated with GUE in dogs undergoing necropsy for all causes with multivariable ORs of 6.3 (95% CI, 2.3-17.3; $P = .0004$) and 3.0 (95% CI, 1.5-5.9; $P = .001$), respectively. Gastrointestinal neoplasia and GI mechanical diseases (foreign bodies or gastric dilatation and volvulus) also were associated with GUE, with multivariable ORs of 13.5 (95% CI, 1.7-108.0; $P = .01$) and 4.8 (95% CI, 1.2-19.7; $P = .03$), respectively. Additionally, after multivariable analysis, the odds of dogs in the AKC working breed group of having GUE were almost 3 times those for mixed breed dogs. Surprisingly, kidney disease, hepatobiliary disease, GI disease (with the exception of mechanical disease), and neoplasia (with the exception of GI neoplasia) were not found to be significantly and independently associated with GUE in this population of dogs undergoing necropsy for all causes.

It seems intuitive that infiltrative GI neoplasia would be a predisposing factor for GUE and this suspicion is supported in the literature. In a retrospective case series, 17 of 82 dogs with GUE had primary GI neoplasia.[1] In another retrospective study of dogs that received blood transfusions for GI bleeding, 13% (7/55) had GI neoplasia.[10] Lymphoma and carcinoma (either gastric or metastatic) were the most common tumor types noted on necropsy in our study population. Mast cell tumors (implicated in GUE based on paraneoplastic hypersecretion of histamine) were not significantly associated with GUE in our study; however, this result could have been because of the relatively small number of dogs with mast cell tumors in our study. Dogs with mast cell tumors have been found to have increased blood histamine concentrations (inversely correlated with gastrin concentrations, suggesting gastric hyperacidity). These findings occur regardless of tumor size, grade, or clinical stage of mast cell tumor, making it difficult to predict which dogs will be affected, and which will develop gastric ulceration.[11] Prospective, case-control studies evaluating the prevalence of GUE in dogs with mast cell tumors may help clarify this relationship. Additionally, no animals in our study were diagnosed with gastrinomas (neuroendocrine tumors that cause GUE by hypersecretion gastrin). These tumors are uncommon, but existing case reports and case series consistently document GUE.[12-14] Thus, their absence from our study population does not preclude gastrinomas as a predisposing factor.

We found the GI mechanical disease (foreign bodies or gastric dilatation and volvulus) was associated with GUE on multivariable analysis, but this association was not significant on univariable analysis (OR, 3.1; 95% CI, 0.8-11.7; $P = .14$). Foreign bodies can cause mechanical trauma to the gastroduodenal mucosa and in a recent study of dogs that had ingested gorilla glue (methylene diphenyl diisocyanate), 3 of 22 had GUE.[15] Physical trauma can lead to GI necrosis and perforation, especially in dogs with linear foreign bodies.[16] The likely mechanism for GUE in dogs with gastric dilatation and volvulus is decreased gastric mucosal perfusion, which also can progress to gastric necrosis.[17]

It is not surprising that administration of NSAIDs or glucocorticoids was associated with GUE because these drugs inhibit prostaglandin synthesis in the GI mucosa, thus directly affecting the protective barrier of the stomach and small intestine. In particular, NSAIDs have been noted as a common potential predisposing factor in previous case series examining GUE and perforation in dogs .[2-4] Indeed, a case series evaluating dogs with gastroduodenal perforation, NSAID administration (at the recommended dosage) was the sole identified potentially predisposing factor in 10/15 dogs.[4] Although these studies contained relatively low numbers of dogs (15-43 dogs) and were descriptive in nature, their findings are consistent with ours. The most commonly used NSAIDs in our study were carprofen, meloxicam, firocoxib, aspirin, and flunixin meglumine. Previous studies have compared the effects of different NSAIDs on the development of GUE in healthy dogs. There is some suggestion that there is a higher risk of producing gastric ulceration with aspirin than with cyclooxygenase 2 selective NSAIDs,[18] whereas other comparisons of multiple NSAIDs (carprofen, meloxicam, and ketoprofen) found no significant difference among NSAIDs for the endoscopic detection of gastroduodenal lesions in healthy dogs.[19] Because of the retrospective nature of our study, we did not examine the effects of individual NSAIDs or their dosages on the extent of GUE.

The role of glucocorticoids alone in causing gastric ulceration has been disputed in the literature. In previous studies, healthy dogs concurrently given NSAIDs and glucocorticoids had increased risk of ulceration.[20,21] In recent prospective, double-blinded studies, healthy dogs had increased risk of endoscopically-identified ulceration when given glucocorticoids. Dogs that received 2 mg/kg/day of prednisone had 7-11 times higher odds of having more severe endoscopic mucosal lesions as compared to dogs that received placebo.[22,23] Our results also support the hypothesis that glucocorticoid treatment alone has ulcerogenic potential. The most commonly administered glucocorticoids in our study included prednisone and dexamethasone. Because of the retrospective nature of the study, we did not attempt to examine the difference in ulcerogenic potential among different types of exogenously administered glucocorticoids. Additional prospective studies may be useful in elucidating any differences in ulcerogenic potential among different types of glucocorticoid medications, the effect of different drug dosages, and the effect of various comorbidities in sick dogs.

It is unclear why working dogs were at increased odds of GUE compared to mixed breed dogs. However, in a previous study, Rottweilers, a breed included in the AKC working dog group, with varied comorbidities were predisposed to gastric perforation.[3] Furthermore, working dogs that engage in strenuous exercise (eg, Alaskan sled dogs) are predisposed to GUE.[24] It is possible that working dogs in our study were more likely to have undertaken strenuous activity, as compared to dogs in the other breed groups. However, because of the retrospective nature of the study, the lifestyle history of these dogs was not available for review. It is also possible that at least some of these dogs had a breed-related predisposition to ulcerogenic disease. Although these dogs also may have been more likely to have received NSAIDs because of their size and proclivity toward orthopedic disease, the multivariable analysis accounted for such a confounding effect.

A diagnosis of lymphoma or leukemia was associated with GUE on univariable analysis, but when glucocorticoid administration was included in multivariable models this association was no longer apparent. This finding indicates confounding (ie, the common administration

of glucocorticoids drugs to dogs with lymphoma or leukemia makes it appear an association exists between these types of neoplasia and GUE when such an association is not present).

We did not find an association between hepatobiliary disease or any of its subcategories including chronic hepatitis and GUE. In previous retrospective case series, hepatobiliary disease was common in dogs with GUE.[2,10] In 1 case series, hepatobiliary disease was diagnosed in 33% of dogs with GUE, but the nature of the hepatobiliary diseases was not described.[2] These studies were descriptive in nature and lacked a control group. The potential pathogenesis of GUE caused by hepatic diseases is poorly understood in dogs. Previously postulated hypotheses include hypergastrinemia secondary to impaired degradation of gastrin by the liver and hemodynamic changes to the gastric mucosa caused by portal hypertension, when present.[25,26] However, another study did not support the occurrence of hypergastrinemia in dogs with hepatic disease.[27] Based on published case series, dogs with intrahepatic portosystemic shunts may be prone to GUE and hemorrhage, and the current recommendation is for these dogs to receive life-long proton pump inhibitor treatment.[7,28] The pathogenesis underlying this finding is also unclear. Our study did not include any dogs with intrahepatic portosystemic shunts and only 1 dog with an extrahepatic shunt in the control group, and thus we cannot rule out the possibility that such dogs are predisposed to GUE. Additional prospective studies regarding the prevalence of GUE in dogs with hepatic disease as a whole, as well as those with intrahepatic portosystemic shunts, are necessary.

Despite the finding in a previous case series, gastrointestinal diseases (with the exceptions of neoplasia, foreign bodies. and gastric dilatation and volvulus) were not associated with GUE in our study.[1,2,9] One of these case series of dogs and cats with idiopathic inflammatory bowel disease noted GUE to be a predominant finding on endoscopic examination.[9] The reason behind this discrepancy is unclear. However, because these previous studies lacked control groups, it is difficult to draw definitive conclusions. Dogs with long-standing, severe inflammatory bowel disease may have been underrepresented in our study, because many dogs with severe GI disease have undergone antemortem diagnostic tests such as endoscopy and GI biopsies and an accurate antemortem diagnosis may decrease an owner's likelihood to pursue necropsy.

The association of kidney disease with GUE in veterinary medicine has been questioned in recent years.[29,30] No association between kidney disease and GUE, neither in regard to antemortem azotemia nor histopathologic findings was found in our study of dogs that underwent necropsy. Although the severity of azotemia and histologic findings in our study were highly variable, previous histologic assessment of dogs with uremic gastropathy as a result of end-stage renal disease did not find a significant relationship with GUE.[30]

In humans, severe systemic disease frequently leads to gastric ulceration by a proposed mechanism of gastric hypoperfusion and ischemia.[31,32] In dogs, the GI tract is a shock organ, and thus blood flow to the GI tract frequently is affected in times of acute or severe illness.[33] Nineteen percent of dogs with GUE were diagnosed with DIC, shock, or sepsis in the week before death whereas only 13.7% of dogs without GUE were diagnosed with these syndromes. However, for many dogs in both the case and control groups, it was not possible to identify DIC, shock, or sepsis from review of the available medical records. Therefore, we were unable to determine if these variables were associated with GUE. Prospective studies of GUE in dogs with critical illness are warranted.

Our study had some limitations. Firstly, although the retrospective design allowed us to enroll a relatively large number of cases and controls, it also had inherent limitations. The lack of standardized diagnostic investigations for patients may have limited our ability to accurately determine the presence of putative predisposing factors. For example, many dogs were diagnosed with "chronic hepatopathies" on necropsy without further description of etiology. Because hepatobiliary diseases are diverse and may not be equivalent in their potential to cause GUE, the numbers of cases in each category may have been insufficient to meaningfully assess their role in GUE. For example, there were difficulties with regard to fully categorizing animals with renal disease. Frequently, their records lacked relevant history to better characterize the azotemia or determine chronicity. In an attempt to overcome this difficulty, we used a combination of both clinicopathologic test results and histologic findings. However, grading chronic kidney disease or acute kidney injury based on existing IRIS guidelines would have been preferred. Many dogs in our study were presented on an emergency basis and euthanized during the same visit. Many of them had not previously been to our hospital and had limited records provided by their primary veterinarian. As such, the categorization of the dogs and their diseases (eg, drug administration, age of the dog) relied upon the history obtained by the emergency clinician and recollections of the owners. By enrolling cases and controls undergoing necropsy for all causes, we were more confident that GUE was accurately identified than if clinical criteria (eg, increased blood BUN-to-creatinine ratio, presence of hematemesis) alone had been used. However, the associations we identified (or did not identify for other putative predisposing factors) in this population of dogs cannot necessarily be extrapolated to the general population of dogs, especially for some of the subcategories with smaller numbers. Given the lack of information in the veterinary literature, we believe our approach was a reasonable initial step that should be followed up with prospective studies.

In conclusion, we determined that NSAID and glucocorticoid administration and GI neoplasia were associated with GUE in dogs undergoing necropsy for all causes. Working dogs undergoing necropsy for all causes also were found to be at increased odds of GUE compared to mixed breed dogs. No significant association was found between hepatobiliary, non-GI, renal, or neoplastic disease and GUE. Prospective studies are warranted to further identify the predisposing factors for GUE in dogs. Dogs receiving NSAIDs or glucocorticoids should be monitored for signs of GUE. The potential predisposition of working breed dogs to GUE requires further investigation.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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